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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/054,678	SKLAR ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *15-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-14 in the response filed August 19, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. The specification should be amended to indicate that parent application, 09/852,967 is now abandoned.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for determining whether an individual has an increased likelihood of having or developing bipolar disorder wherein the method comprises performing an inheritance study wherein an individual that is the offspring of a parent having bipolar disorder is analyzed for the inheritance of a haplotype consisting of an A at nucleotide position 476, a G at nucleotide position 942 and a C at nucleotide position 1635 of the dopamine beta-hydroxylase gene (DBH) gene and wherein the inheritance of said haplotype is indicative of an increased likelihood that the individual will have or will develop bipolar disorder, and while the prior art enables methods for identifying cocaine-dependent subjects at an increased risk of developing cocaine-

induced paranoia by detecting the haplotype of DBH*444A and DBH*5- del, does not reasonably provide enablement for methods of diagnosing any neuropsychiatric disorder in an individual by detecting any one of an A at nucleotide position 476, a G at nucleotide position 942 or a C at nucleotide position 1635 of the DBH gene as indicative of an increased likelihood that said individual will have or will develop a neuropsychiatric. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn to methods for diagnosing or aiding in the diagnosis of a neuropsychiatric disorder wherein the method comprises determining the nucleotide at any one or more of the positions 476, 942 or 1635 of the dopamine beta-hydroxylase gene wherein the presence of any one of an A at nucleotide position 476, a G at nucleotide position 942 or a C at nucleotide position 1635 of the DBH gene is indicative of an increased likelihood that said individual has or will develop a neuropsychiatric disorder or wherein the presence of any one of a G at nucleotide position 476, a T at

nucleotide position 942 or a T at nucleotide position 1635 of the DBH gene as indicative of a decreased likelihood that said individual has or will develop a neuropsychiatric.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the state of the art of diagnosing a neuorpsychiatric disorder by detecting a polymorphism is highly unpredictable and the specification has not provided sufficient guidance to enable the skilled artisan to practice the invention as it is broadly claimed for the reasons set forth below.

The specification (see, for example, page 7) provides the results of a study of the transmission of DBH polymorphisms to offspring diagnosed as having bipolar disorder. The study found that the haplotype consisting of an A at nucleotide position 476, a G at nucleotide position 942 and a C at nucleotide position 1635 of the DBH gene was transmitted to offspring diagnosed as having bipolar disorder more often "than would be expected by chance." The specification (page 7) also states that "(t)hus it appears that

the less common allele (the variant allele) of each of the three SNPs may contribute to protection or reduction in symptomology with respect to neuropsychiatric disorders, while the more common allele (the reference allele) of each of the three SNPs may predispose an individual to a neuropsychiatric disorder or to increased symptomology of these disorders. The association is particularly strong when two or more of the alleles are considered in combination, and strongest when all three alleles are considered in combination." However, the specification does not provide any information on the transmission of each of the alleles individually to affected offspring or on the transmission of 2 alleles to offspring. The specification only provides information on the transmission of the full haplotype of the 3 polymorphisms of an A at nucleotide position 476, a G at nucleotide position 942 and a C at nucleotide position 1635 of the DBH gene. Additionally, the specification does not provide any information on the general occurrence of the haplotypes or individual alleles in the general population versus an affected population. There are no teachings in the specification as to how to apply the claimed method to the general population by detecting the haplotypes or single alleles in any individual as indicative of a neuropsychiatric disorder. As indicated in the specification, the alleles found to be associated with inheritance of bipolar disorder are the alleles that are the most prevalent in the general population. For example, Cubells (American Journal of Medical Genetics (1997)) teaches that the DBH*304A allele (i.e., the alanine allele; referred to in the specification as the DBHu1 G allele) was the most common allele in all populations tested, with allele frequencies greater than 0.80. If one practiced the claimed invention as written, then one would conclude that at least 80%of

the individuals in the general population had an increased likelihood of having a neuropsychiatric disorder. Such a finding is not consistent with the actual prevalence of these disorders in society. Cubells (see abstract) goes on to state that there is significant heterogeneity in the frequency of the allele across different populations and that this "demonstrates the importance of controlling for population stratification in future studies testing for associations between DBH*304S and clinical phenotypes." There are no specific teachings or examples in the specification of using the claimed methods to detect the occurrence or susceptibility to neuorpsychiatric disorders in the general population by analyzing DBH nucleic acids from any member of the population for the occurrence of one or more of the DBH polymorphisms at positions 476, 942 or 1635. In view of the teachings of Cubells and the lack of information provided in the specification, it is highly unpredictable as to whether a method which detects the most prevalent form of each allele could be used to detect that allele as indicative of an individual having or being susceptible to developing a neuropsychiatric disorder.

Secondly, the specification has not enabled methods which detect susceptibility to any psychiatric disorder. As discussed above, the specification provides only the results of a study showing the transmission of the haplotypes in individuals with bipolar disorder. There is no information provided in the specification as to the prevalence or transmission of the individual alleles or the haplotypes in other neuropsychiatric disorders. There are also no teachings in the specification as to a universal association between the alleles and neuropsychiatric disorders or any information as to the mechanism by which the presence of the polymorphisms would be lead to a

neuropsychiatric disorder. Furthermore, the specification does not exemplify any methods in which a neuropsychiatric disorder other than bipolar disease is diagnosed by detecting one or more of an A at nucleotide position 476, a G at nucleotide position 942 and a C at nucleotide position 1635 of the DBH gene. Accordingly, it is highly unpredictable as to whether the presence of the individual DBH alleles or the DBH haplotypes could be detected as indicative of any neuropsychiatric disorder, such as schizophrenia, schizoaffective disorder, recurrent unipolar depression, hypomania, mood disorders, anxiety disorders, ADHD, Tourette's syndrome, any addictive disorder, any substance use disorder, any substance abuse disorder or any disorder related to blood pressure. The unpredictability of the claimed method is supported by the teachings in the art. For example, Cubells (Molecular Psychiatry (2000) 5: 56-63) teaches that there was no significant differences between the frequency of the DBH*444g/a allele in healthy European Americans as compared with individuals in a cocaine-dependent group. Accordingly, Cubells essentially teaches that in the general population, the DBH*444 A allele (i.e., an A at nucleotide position 476) is not associated with risk of cocaine-dependency (i.e.., substance abuse or substance use). Cubells did find that the DBH*444g/a alleles were in linkage disequilibrium with DBH*5-ins-del alleles. At page 60, Cubells teaches that "(n)either DBH*5'-del or DBH*444a alone significantly associated with cocaine-induced paranoia, presumably because some of the alleles at each individual polymorphism occurred on different haplotypes backgrounds, and were therefore in weaker LD with low-DBH functional variants." Additionally, the cocaine-dependent group did not exhibit differences in DBH haplotype

(DBH*5-ins/del and DBH*444a/g) frequencies when compared to normal European Americans. However, when the cocaine-dependent group was divided into paranoia (+) and paranoia (-) individuals, it was found that the DBH*5 del / DBH*444 a haplotype was more prevalent in paranoia (+) versus paranoia (-) cocaine users. Accordingly, Cubells highlights the unpredictability of applying the claimed method to the general population and the unpredictability of determining susceptibility to neuropsychiatric disorders by analyzing a single DBH polymorphism. The unpredictability in the art is further emphasized by the teachings of Kirov (Molecular Psychiatry (1999) 4: 558-565. Kirov (see page 559, 561 and abstract) reports that the DBH*304A polymorphism (i.e., the DBHu1 polymorphism at position 942) was not found to be associated with transmission or occurrence of bipolar disorder. Williams (American Journal of Medical Genetics (1999) 88:557-559) teaches that the DBHu1 polymorphism is not associated with susceptibility to schizophrenia. Cubells (Society for Neuroscience Abstracts. November 2000. 26(1-2): page 1161, abstract 436.1) teaches that the while the DBH*444A (position 476) polymorphism is associated with lower plasma DBH levels, the polymorphism was not associated with unipolar psychotic depression. Houy et al. (American Journal of Human Genetics. August 2000. 96: 528, abstract P208) teaches that the Ala-304-Ser polymorphism (DBHu1 polymorphism at position 942) is not associated with deficit schizophrenia. Iwata (American Journal of Medical Genetics. January 2003. 116B:23-26) were also unable to find an association between the Ala-304-Ser polymorphism and early-onset schizophrenia. Additionally, Payton (American

Journal of Medical Genetics (2001) 105: 464-470) reported that the DBHu1 polymorphism was not associated with attention-deficit hyperactivity disorder.

Accordingly, in view of the lack of specific guidance and teachings provided in the specification and in view of the unpredictability in the art, undue experimentation would be required to practice the methods as they are broadly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 6, 7, 10, 11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cubells (Molecular Psychiatry (January 2000) 5: 56-63).

Cubells (page 60) teaches that in individuals with cocaine dependency, the haplotype of the DBH*444A allele (i.e., an A at position 476), together with the DBH*5-

del allele, is associated with the occurrence of paranoia, as compared to cocaine-dependent subjects without paranoia. Cubells also teaches methods for detecting the presence of the DBH*444A and DBH*5- del alleles (see pages 57-58). Cubells does not teach diagnosing susceptibility to or the occurrence of cocaine-induced paranoia by detecting the DBH*444A allele together with the DBH*5-del allele. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Cubells for detecting the DBH*444A and DBH*5- del alleles for the diagnosis of cocaine-induced paranoia in order to have provided a rapid method for the identification of cocaine-dependent individuals who more susceptible to having or developing psychotic symptoms.

It is noted that the claims as broadly written are inclusive of methods which detect the DBH*444A (476A) allele together with another DBH allele. Additionally, the claims are inclusive of methods which diagnose an increased likelihood of having any neuropsychiatric disorder such as addictive disorders, substance use disorders or substance abuse disorders, which each thereby encompass cocaine-dependent paranoia.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers
November 13, 2003

CARLA J. MYERS
PRIMARY EXAMINER